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# **Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases Guidance for Industry**

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**August 2017  
Clinical/Antimicrobial**

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# **Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases Guidance for Industry<sup>1</sup>**

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

## **I. INTRODUCTION**

This guidance is intended to assist sponsors in the clinical development of new antibacterial drugs.<sup>2</sup> Specifically, the guidance explains the FDA's current thinking about possible streamlined development programs and clinical trial designs for antibacterial drugs to treat serious bacterial diseases in patients with an unmet medical need, including patients who have a serious bacterial disease for which effective antibacterial drugs are limited or lacking.<sup>3</sup> Antibacterial drugs that are *pathogen-focused* can be developed for the treatment of serious bacterial diseases in patients who have an unmet medical need.<sup>4,5</sup>

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<sup>1</sup> This guidance has been prepared by the Division of Anti-Infective Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

<sup>2</sup> For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products regulated in CDER unless otherwise specified.

<sup>3</sup> For example, effective antibacterial drugs can be limited because resistance to several antibacterial drugs has developed. Patients who have allergies or intolerance to several antibacterial drugs also may be considered as having an unmet medical need. See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*, section III.C., Unmet Medical Need. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>4</sup> Given the wide range of meanings associated with the terms *pathogen-focused*, *pathogen-specific*, *organism-specific*, or *pathogen-based* antibacterial drugs, we recommend that sponsors provide a clear description of their proposed drug development program. For purposes of general discussion in this guidance, the term *pathogen-focused antibacterial drug* refers to a drug active against only a single species or few species within a genus of bacteria.

<sup>5</sup> For a detailed discussion of regulatory programs intended to streamline or expedite development and review of drugs (e.g., fast track, breakthrough) and their attendant criteria and definitions, see the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

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We note that section 3042 of the 21st Century Cures Act (Public Law 114-255), which establishes a limited population pathway for certain antibacterial and antifungal drugs (LPAD) that are intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs, was enacted shortly before publication of this guidance.<sup>6</sup> Some antibacterial drugs that are candidates for a streamlined development program may also be candidates for LPAD. We intend to issue separate guidance regarding LPAD. Sponsors are encouraged to discuss proposed approaches with the Division of Anti-Infective Products.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.<sup>7</sup>

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## **II. BACKGROUND**

Antibacterial drug resistance continues to be a public health concern. It has led to an increasing number of patients with serious bacterial diseases, such as hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, and complicated urinary tract infections, who may not respond to currently available antibacterial drugs.<sup>8</sup>

Conducting clinical trials to evaluate antibacterial drugs for the treatment of patients with a serious bacterial disease can be challenging for a number of reasons, including: (1) the need to promptly initiate empiric antibacterial therapy to reduce the risk of morbidity and mortality, which may obscure the effect of the antibacterial drug under study because empiric antibacterial therapy administered to some patients before enrollment in the trial may be effective; (2) the severity of the acute illness in patients (e.g., delirium in the setting of acute infection) may make obtaining informed consent and performing other trial enrollment procedures difficult; (3) the diagnostic uncertainty with respect to the etiology of the patients' underlying disease, including the specific bacterial etiology; and (4) the potential need for concomitant antibacterial drug therapy (often empiric) with a spectrum of activity that may overlap with the activity of the antibacterial drug being studied can make assessment of the efficacy of the investigational drug difficult.

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<sup>6</sup> See section 506(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Guidance regarding LPAD will be issued at a later date as required in section 506(h)(5) of the FD&C Act (as amended by the 21st Century Cures Act).

<sup>7</sup> We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>8</sup> See the Bibliography at the end of this guidance.

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Given these challenges associated with the development of new antibacterial drugs for the treatment of serious bacterial diseases, we are exploring approaches that may help streamline development programs for antibacterial drugs that could address an unmet medical need. As recognized in FDA regulations for the evaluation of drugs intended to treat life-threatening and severely debilitating illnesses:

*“The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from drugs that treat life-threatening and severely-debilitating illnesses, than they would accept from drugs that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated.”<sup>9</sup>*

Sponsors are encouraged to discuss with the FDA innovative trial designs and statistical analysis strategies that could help to streamline clinical development of new antibacterial drugs.

### **III. QUESTIONS AND ANSWERS**

The following questions and answers are provided to explain the FDA’s current thinking on streamlined development programs that may be appropriate for development of antibacterial drugs to treat serious bacterial diseases in patients with unmet medical need.

#### **1. What types of antibacterial drugs may be appropriate for a streamlined development program?**

Candidates for a streamlined development program are antibacterial drugs intended to treat serious bacterial infections in patients who have few or no available treatments.<sup>10</sup> Such drugs are likely to have: (1) a new mechanism of action that preserves antibacterial activity against bacteria that have mechanisms of resistance to other available antibacterial drugs; (2) an added inhibitor that neutralizes a mechanism of resistance; (3) an alteration in the structure of the molecule that makes the drug no longer susceptible to the mechanisms of resistance to existing drugs; or (4) some other characteristic that has a potential to lead to enhanced effectiveness. A drug that has slightly greater potency (e.g., more active by 2- to 3-fold dilutions based on in vitro testing) generally would not be considered a drug that addresses an unmet need and should undergo a traditional development program.

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<sup>9</sup> See 21 CFR 312.80.

<sup>10</sup> For a more general discussion of the concepts of *unmet medical need* and *serious conditions*, see the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

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### **2. Can a drug that treats a single species of bacteria be a candidate for a streamlined development program?**

Yes, a drug that treats a single species (or a few species) of bacteria is a possible candidate for a streamlined development program. For an antibacterial drug active against only a single species (or few species) within a genus, possible clinical trial design recommendations are discussed below. When the single species is an infrequent cause of infection, sponsors should discuss possible development approaches with the FDA. When planning for a streamlined drug development program, sponsors should consider the following factors for clinical trials:

- The frequency with which the bacterial species of interest causes serious infections
- The use and availability of rapid diagnostic tests to promptly identify patients with the bacterial etiology of interest as the cause of their infection
- The codevelopment of a rapid diagnostic test for use in clinical practice<sup>11</sup>

### **3. What are important nonclinical considerations in a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and an unmet medical need?**

In the early stages of development, sponsors generally conduct nonclinical evaluations of an investigational antibacterial drug to answer questions about antibacterial activity, mechanism of action, mechanism(s) of resistance to the new drug, and whether the new drug is affected by mechanisms that confer resistance to other drugs. In addition, information about chemistry, manufacturing, and controls and nonclinical toxicology studies are expected to be included in an investigational new drug application.<sup>12</sup>

During nonclinical development, sponsors should characterize the properties of the new antibacterial drug and assess its potential as a candidate for the treatment of patients with serious infections and few or no treatment options. To the extent that a streamlined clinical development program involves smaller, shorter, or fewer clinical trials, it is likely that less safety data will be generated, and the nonclinical studies may assume an even more important role in contributing to the evaluation of the safety of an antibacterial drug. Thus, the nonclinical evaluations should not be smaller or streamlined. A sponsor developing a drug using a streamlined clinical development program must still provide adequate data to demonstrate that the drug is safe and

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<sup>11</sup> The Center for Devices and Radiological Health regulates devices for the purpose of use in the clinical care of patients. Sponsors should discuss with the FDA whether an investigational in vitro diagnostic device is intended to be used with a corresponding drug as a companion diagnostic device. See the guidance for industry and Food and Drug Administration staff *In Vitro Companion Diagnostic Devices* and the draft guidance for industry and Food and Drug Administration staff *Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices* (when final, this guidance will represent the FDA's current thinking on this topic).

<sup>12</sup> See 21 CFR 312.23.

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effective to meet the statutory standards for approval.<sup>13</sup> Other guidances for industry discuss in more detail these important elements of nonclinical development considerations.<sup>14</sup>

For streamlined drug development programs addressing unmet medical needs for serious bacterial infections, sponsors should provide the following important nonclinical information about the investigational drug:

- In vitro activity of the investigational drug, including the minimum inhibitory concentration (MIC) from a representative sample of target bacterial pathogens
- Activity in appropriate animal models of infection
- Evidence for the antibacterial drug's ability to achieve appropriate levels in relevant tissue sites from nonclinical studies (e.g., from appropriate animal models of infection)
- The mechanism of action and whether mechanisms of resistance to other drugs affect its antibacterial activity
- The evaluation of pharmacokinetic/pharmacodynamic (PK/PD) relationships from animal models of infection, such as the PK/PD index that is associated with efficacy in a relevant animal model and/or in vitro model(s) based on: (1) the area under the unbound plasma concentration time curve over the MIC; (2) maximum unbound plasma concentration over the MIC; (3) time above the MIC; or (4) other appropriate metrics
- The target value of the PK/PD index that is associated with efficacy in the animal model
- Dose and frequency of administration that was evaluated in in vitro models of infection based on PK parameters obtained from human PK studies

#### **4. What are clinical trial design considerations in a streamlined development program?**

Different approaches can be used to evaluate an antibacterial drug for the treatment of a serious bacterial disease in patients with an unmet medical need. The approaches outlined below are provided as examples that sponsors may consider using. These approaches are neither exhaustive nor mutually exclusive; in some cases combining elements from different approaches may be appropriate. Sponsors are encouraged to discuss their specific proposed development

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<sup>13</sup> See 21 U.S.C. 355(d).

<sup>14</sup> See, for example, the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and *S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals*, and the guidances for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* and *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information*.

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programs with the FDA before commencing clinical trials. The following are examples of trial design considerations.

### **a. Noninferiority clinical trials**

The efficacy of an investigational drug intended to treat serious bacterial diseases in patients with an unmet medical need can be established on the basis of a noninferiority trial in a population of patients who have treatment options for their serious bacterial disease. The trial population should include patients with severity of illness and/or comorbid conditions that are similar to those of patients who have an unmet medical need to have a finding of safety and efficacy that can be relevant to the patient population with unmet medical need (i.e., patients with infections caused by bacteria resistant to other available antibacterial drugs).<sup>15,16,17</sup>

Given that the antibacterial drug would be indicated for use only for patients who have limited or no treatment options, the characterization of efficacy in a noninferiority trial could be based on a larger noninferiority margin than is typically recommended in infectious disease-specific guidances but still establishes effectiveness.<sup>18</sup> The labeled indication would specifically state that the drug should be reserved for patients who have limited or no alternative treatment options (see the response to Question 17).

Because there usually will be few patients, if any, who have an unmet medical need in the noninferiority trial, sponsors may want to consider an additional clinical trial in patients with an unmet medical need.<sup>19</sup> The additional clinical trial can be conducted in patients with the specific

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<sup>15</sup> Patients with unmet need may have greater comorbidities, altered pharmacokinetics, or disease severity that affect treatment effect and patient outcomes. Enrolling patients with these characteristics in the noninferiority trial should increase the generalizability to similar populations of patients who have unmet need.

<sup>16</sup> A hierarchical nested noninferiority/superiority analysis can be considered if a sufficient number of patients with infection caused by bacteria resistant to the control drug are expected to be enrolled in the trial. See the response in Question 4.c., Nested noninferiority/superiority clinical trials.

<sup>17</sup> If the investigational drug is shown to be effective in treating a particular type of infection caused by certain bacteria, it should remain effective as long as the bacteria causing the infection are susceptible to the investigational drug. If these bacteria are susceptible to the investigational drug, that they are resistant to other antibacterial drugs generally does not affect the efficacy of the investigational drug. As noted, it is important to enroll patients with severity of illness and/or comorbid conditions comparable to patients with unmet medical need so that results are generalizable.

<sup>18</sup> For example, the guidance for industry *Complicated Urinary Tract Infections: Developing Drugs for Treatment* recommends a noninferiority margin of 10 percent for a trial evaluating a new antibacterial drug based on reliable and reproducible evidence of an antibacterial drug treatment effect of approximately 30 percent (the effect of the antibacterial drug over placebo). An active-controlled trial showing noninferiority based on the selection of a noninferiority margin greater than 10 percent but less than the treatment effect of 30 percent (e.g., a noninferiority margin of 15 percent) still establishes effectiveness for the treatment of complicated urinary tract infection but allows for a greater potential loss of efficacy. Such a finding of noninferiority could be acceptable for patients who have limited or no alternative treatment options for their serious infectious disease.

<sup>19</sup> See, for example, the “Tier B” paradigm in Rex JH, BI Eisenstein, J Adler, et al., 2013, A Comprehensive Regulatory Framework to Address the Unmet Need for New Antibacterial Treatments, *Lancet Infect Dis*, 13(3):269-273.

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type of infection studied in the noninferiority trial as well as other types of infections of comparable or greater disease severity. Ideally, a randomized active-controlled trial is the best option, if active control therapy is feasible and ethical, because then comparative safety and efficacy evaluations can be performed. Experience has shown that having a randomized comparator group can be particularly important for interpreting safety data from the trial (in small trials that enroll acutely ill patients, having a comparator group can help in evaluating adverse events that may represent background adverse events in this ill population). This trial does not have to be powered for inference testing. If demonstrating statistical superiority is planned, refer to the response in Question 4.b., Superiority clinical trials.

The additional clinical trial should collect information on patient comorbidities, disease severity, and pharmacokinetics, with comparisons to the patient population in the noninferiority trial (see the response to Question 7 regarding PK/PD considerations).

### **b. Superiority clinical trials**

An investigational drug can be compared to best-available active control therapy in a single randomized controlled superiority trial. Sponsors should discuss with the FDA the type of trial design (e.g., a trial enrolling patients who have a particular type of infection (e.g., ventilator-associated bacterial pneumonia) or who have different types of infection (e.g., ventilator-associated bacterial pneumonia and complicated intra-abdominal infection)) and inferential statistical evaluations for a finding of superiority.

There may not be sufficient historical experience to clearly establish a reliable and reproducible treatment effect of the best available active control antibacterial drug therapy against placebo or no treatment. However, it is likely that it has a treatment effect greater than placebo or no treatment. Given this likelihood, it may be difficult to show unequivocal superiority for the investigational drug and it may be appropriate to use a less stringent statistical finding for superiority. In this case, an efficacy finding less robust than usual would be accepted as evidence of efficacy to enable the drug to be marketed because of the identified unmet medical need.

A superiority trial design can be used to evaluate an antibacterial drug with activity against a single species (or a few species) of bacteria. A sufficient number of patients for enrollment into a trial of a particular type of infection (e.g., ventilator-associated bacterial pneumonia) may not be available. Patients with infections at more than one body site caused by the bacterial species of interest can be enrolled in the trial, with inferential statistical testing for superiority.

A superiority clinical trial design that relies on an external control population may be appropriate to evaluate efficacy when the untreated morbidity and/or mortality is high and does not vary widely in the patient population with unmet medical need, and the effect of the investigational drug in an unmet medical need population is expected to be large.<sup>20</sup> For an externally controlled trial, the control patients should be as similar as possible to the population expected to receive the investigational drug. Patients should have been treated in a similar setting and in a similar time frame, except with respect to the investigational drug therapy. For sponsors considering an

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<sup>20</sup> See ICH E10.

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externally controlled trial, we recommend randomizing at least a small number of patients to the active control (e.g., through disproportionate randomization of 4:1), if feasible and ethical based on an active control considered to be best-available therapy. This will allow for an assessment of the comparability of the external control to the trial population. Frequentist and Bayesian statistical methods can then be used to combine external control data with data from the patients randomized to the active control in assessing differences between treatment groups for the primary comparison.

### **c. Nested noninferiority/superiority clinical trials**

Patients with and without unmet medical need can be included in a nested, active-controlled noninferiority/superiority trial design. Patients should be randomized to the investigational drug or the control drug before the availability of the results of antibacterial drug susceptibility testing of the bacteria causing the patient's infection because of the time required for results from susceptibility testing to become available using current technologies. The trial should include provisions for adjusting the control regimen to provide standard-of-care treatment for patients who are found to have resistant bacterial isolates at baseline. It is essential that adequate procedures be in place to protect patients enrolled in this trial from avoidable exposure to less effective therapy.

In this trial design, the first step should be to demonstrate noninferiority of the investigational drug to the control treatment in the population of patients who have a baseline bacterial isolate susceptible to the control drug. The second step should be to evaluate superiority in patients subsequently confirmed to be infected with a baseline bacterial isolate resistant to the control drug.<sup>21</sup> This type of hierarchical nested design does not require any multiplicity adjustments to control the overall type I error rate.<sup>22</sup> Given the sequential nature of the preplanned testing, a noninferiority test followed by testing for superiority, there would be no statistical penalty for the superiority evaluation.

### **5. Can patients who have infections at different body sites be enrolled in the same clinical trial? If so, what are examples of primary efficacy endpoints and analysis considerations?**

Yes. The trials should be designed as superiority trials in patients with an unmet medical need. These trials should be considered when factors preclude the enrollment of patients in trials of infections at a single body site; for example, an antibacterial drug with activity against a single species (or a few species) of bacteria.

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<sup>21</sup> See, for example, the nested noninferiority/superiority design in Infectious Diseases Society of America, 2012, White Paper: Recommendations on the Conduct of Superiority and Organism-Specific Clinical Trials of Antibacterial Agents for the Treatment of Infections Caused by Drug-Resistant Bacterial Pathogens, *Clin Infect Dis*, 55(8):1031-1046.

<sup>22</sup> See Huque MF, T Valappil, and G Soon, 2014, Hierarchical Nested Design for Demonstrating Treatment Efficacy of New Antibacterial Drugs in Patient Populations With Emerging Bacterial Resistance, *Statistics in Medicine*, first published online 23 June 2014, DOI: 10.1002/sim.6233.

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There may be several options to consider for a primary efficacy endpoint for this trial design. One option is to use different clinical efficacy endpoints based on each body site infection. For example, patients who have complicated intra-abdominal infections would be evaluated on the clinical success outcome at day 28 after randomization, and patients who have complicated urinary tract infections would be evaluated on the responder outcome at 7 days after completion of antibacterial drug therapy. Thus, each patient would be counted as a *success* or *failure*, depending on the outcome specific to each body site infection and results would be examined by each body site (recognizing the limited numbers available for each site). Another option for a primary efficacy endpoint is all-cause mortality if the types of infections in the trial are often fatal when untreated.

A streamlined development program that includes a trial enrolling patients with infections at different body sites may have reduced capacity to detect relative deficits in performance of an antibacterial drug in some body sites compared to others. There have been several recent instances where unexpected results from clinical trials revealed deficits in the performance of an antibacterial drug.<sup>23</sup> Trials should enroll patients who have greater severity of illness and similar comorbid conditions to minimize concerns regarding the potential for deficits in performance in some body sites.

For example, such a trial of an investigational drug with activity against gram-negative bacteria should enroll patients receiving care in an intensive care unit with one of the following different body site infections: (1) ventilator-associated bacterial pneumonia; (2) hospital-acquired bacterial pneumonia requiring mechanical ventilation; (3) complicated intra-abdominal infection plus hypotension and/or bacteremia; and (4) complicated urinary tract infection plus hypotension and/or bacteremia. In this example, we recommend that patients who have ventilator-associated bacterial pneumonia or hospital-acquired bacterial pneumonia requiring mechanical ventilation should comprise approximately 50 percent or more of the total patient population. Sponsors are encouraged to bring any plans for multisite studies to the FDA before they begin to ensure that a proper mix of patients is obtained.

Frequentist (e.g., logistic regression models) or Bayesian modeling approaches for assessing subgroup-specific treatment effects may be useful in trials designed to enroll patients with body site infections that have different severity and associated comorbid conditions. Modeling approaches provide a measure of internal consistency of treatment effect among the subgroups of each body site.

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<sup>23</sup> See, for example, FDA Statement on a terminated clinical trial with Doribax (doripenem): Safety Announcement: [01-05-2012] (available at <http://www.fda.gov/Drugs/DrugSafety/ucm285883.htm>); FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning: Safety Announcement: [9-27-2013] (available at <http://www.fda.gov/drugs/drugsafety/ucm369580.htm>); Pertel PE, P Bernardo, C Fogarty, P Matthews, et al., 2008, Effects of Prior Effective Therapy on the Efficacy of Daptomycin and Ceftriaxone for the Treatment of Community-Acquired Pneumonia, *Clin. Infect. Dis.*, Apr 15, 46(8):1142-51, doi: 10.1086/533441.

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### **6. What are examples of statistical approaches or randomization strategies in a streamlined clinical program?**

Group sequential designs can be useful and flexible for early stopping based on efficacy or futility. Adaptive design clinical trials or trial designs with features, such as those discussed below, can be considered.<sup>24</sup>

A cluster randomization strategy is one possible approach that could be explored. With appropriate informed consent procedures, cluster randomization may facilitate trial conduct by allowing for streamlined enrollment procedures. Consenting patients enrolled at sites randomized to the standard-of-care arm would be treated consistent with the standard of care at that site, while consenting patients enrolled at sites randomized to the investigational drug arm would be treated with the investigational drug. This strategy is best suited for trials with a large number of clinical centers, each enrolling a relatively small number of patients per site. With adequate numbers of clinical centers, randomization should ensure balance between the treatment groups with respect to both site and patient-level characteristics.

Clinical trial networks also might foster trial conduct and feasibility for evaluating new antibacterial drugs. Innovative clinical trial approaches in which several different investigational drugs could be included, each as different treatment arms in the trial and compared to a control arm representing standard-of-care treatment, are also possibilities that could be considered.<sup>25</sup>

Collaboration between sponsors may streamline development of antibacterial drugs with spectra of activity that do not overlap. For instance, if investigational Drug A and investigational Drug B are active against different species of bacteria, and use of Drug A and Drug B together could be considered as complete empiric coverage for possible bacterial pathogens causing the infection, then a trial comparing Drug A plus Drug B to the best-available active control therapy could be used to evaluate each drug in the prespecified primary analysis populations based on the baseline bacterial species. Sponsors pursuing this approach should discuss with the FDA the safety data that would be needed to assess the individual antibacterial drugs.

Factorial designs are another consideration. Clinical trials are often conducted in intensive care units to evaluate interventions whose mechanisms of action differ from antibacterial drugs (e.g., anti-inflammatory therapies). A factorial design would simultaneously randomize patients in such a trial to one of two different antibacterial drug regimens and one of two different nonantibacterial interventions, and thus allow the single trial to answer two questions. Sponsors interested in using a factorial design should discuss with the FDA whether any interactions are expected between the antibacterial and nonantibacterial interventions.

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<sup>24</sup> Clinical trial designs with adaptive features may enhance the efficiency of the trial; sponsors who are considering an adaptive design are encouraged to consult the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*. When final, this guidance will represent the FDA's current thinking on this topic.

<sup>25</sup> An example of an innovative trial design is the **Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And MoLecular Analysis 2 (I-SPY 2 TRIAL)**. Information about the trial can be found at <http://www.ispytrials.org/home>.

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### **7. What is the importance of PK/PD (exposure-response) data in a streamlined development program?**

Information on the distribution of MIC for the relevant bacteria based on recent surveillance data, the results of PK/PD (exposure-response) assessments in animals, and results from human PK trials should be integrated to help identify the appropriate dose and frequency of administration for evaluation in clinical trials.<sup>26</sup> In some previously conducted clinical trials, wide variability in exposure was seen in patients with unmet need compared to those enrolled in a noninferiority trial at a body site of infection. Additionally increased variability in exposure has also been noted by the type of infection (e.g., ventilator-associated bacterial pneumonia). Thus, it is important that adequate evaluation of the PK and dose justification be provided for patients with unmet need who have the infection type to be evaluated. PK information from humans should include information about the distribution of the drug to the site of action (e.g., epithelial lining fluid). Comparison of human and animal exposure data should include correction for any differences in plasma protein binding.

Collection of PK data in clinical trials (e.g., sparse sampling in all patients enrolled in clinical trials) may help address potential questions about efficacy or safety that arise and help describe the effects of intrinsic and extrinsic factors on pharmacokinetics and pharmacodynamics. Patients with serious bacterial diseases with an unmet medical need often have important comorbidities, notably renal or hepatic impairment, and, therefore, an increased likelihood of alterations in pharmacokinetics. An important consideration in the conduct of trials is to characterize pharmacokinetics in such patients (see the response in Question 4.a., Noninferiority clinical trials, regarding an additional clinical trial in patients with an unmet medical need). For example, understanding the pharmacokinetics of the investigational drug in patients with renal or hepatic impairment early in development could facilitate enrollment in clinical trials of such patients (e.g., by providing guidance on dosing).

### **8. What is the size of the premarketing safety database in a streamlined development program?**

The premarketing safety database of an investigational drug should be adequate in light of its potential benefit. In general, a safety database for a drug that is the subject of a streamlined development program should include approximately 300 patients at the dose and duration of therapy proposed for marketing. This safety database could include patients from all phases of clinical development, and include patients who do not have an unmet medical need.<sup>27</sup>

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<sup>26</sup> See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* and the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration*.

<sup>27</sup> Nonclinical data and early safety data can inform the size of the premarketing safety database; see, for example, ICH guidances for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* and *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs — Questions and Answers (R1)*.

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### **9. What other safety regulatory requirements should be considered in a streamlined development program?**

Section 901 of the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85) created sections 505(o) and 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Section 505(o)(3) of the FD&C Act authorizes the FDA to require certain postmarketing studies and clinical trials for prescription drug products.<sup>28</sup> Section 505-1 authorizes the FDA to require a risk evaluation and mitigation strategy (REMS) if the FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug.<sup>29</sup>

As described earlier, a streamlined development program may include a relatively small safety database. In some instances, this may lead to uncertainties about findings of a potential serious risk (e.g., strength of the association of the risk with drug treatment; the rate of occurrence of the risk). In these cases, when the approval standard has been met, the FDA may determine that a postmarketing study or clinical trial is needed to further characterize the risk.

### **10. Will the FDA accept greater toxicity for drugs that treat patients who have a serious bacterial disease and an unmet medical need?**

The safety of a drug is assessed by weighing its risks against its benefits. Drugs with risks that would be unacceptable for a broad population may be acceptable for patient populations with serious disease that do not have other treatment options. As stated previously, acceptance of greater uncertainty or higher risk in patients with serious diseases and with an unmet need is an appropriate approach to the risk-benefit assessment.<sup>30</sup> Some antibacterial drugs may also be candidates for the LPAD pathway established under section 3042 of the 21st Century Cures Act (Public Law 114-255).<sup>31</sup> The FDA intends to issue separate guidance regarding LPAD. Sponsors are encouraged to discuss proposed approaches with the Division of Anti-Infective Products.

### **11. Does a streamlined development program for antibacterial drugs result in a lower regulatory standard for drug approval?**

No. Drugs approved on the basis of a streamlined development program must meet the statutory standards for safety and effectiveness set forth in section 505(d) of the FD&C Act. A finding of effectiveness must be supported by substantial evidence based on adequate and well-controlled

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<sup>28</sup> For further information on the FDA's current thinking on this topic, see the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(0)(3) of the Federal Food, Drug, and Cosmetic Act*.

<sup>29</sup> For further information on REMS, see the draft guidance for industry *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*. When final, this guidance will represent the FDA's current thinking on this topic.

<sup>30</sup> See 21 CFR 312.80, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses.

<sup>31</sup> See section 506(h)(2) of the FD&C Act (as amended by the 21st Century Cures Act).

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clinical investigations.<sup>32</sup> A finding of safety must be supported by sufficient information (including adequate tests) to determine whether the drug is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling.<sup>33</sup>

As noted previously, use of a streamlined antibacterial drug development program is consistent with the philosophy first formally articulated in regulations codified at part 312, subpart E (21 CFR part 312).<sup>34</sup> This philosophy reflects the FDA's commitment to expediting the availability of drugs for serious diseases for patients as soon as it can be concluded that the drug's benefits exceed its risks, especially when these patients have unmet needs, while preserving appropriate standards for safety and effectiveness.

This guidance is not intended to establish a new approval pathway or standard for antibacterial drugs. As noted above, the LPAD pathway was recently established under section 3042 of the 21st Century Cures Act (Public Law 114-255). The FDA intends to issue separate guidance regarding LPAD. Sponsors are encouraged to discuss proposed approaches with the Division of Anti-Infective Products.

### **12. Why is it important for the FDA and for sponsors to emphasize to the health care community the risks and benefits of drugs developed under a streamlined development program for the treatment of serious bacterial diseases in patients with an unmet medical need?**

To obtain approval, a sponsor must demonstrate that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling (section 505(d)(1) of the FD&C Act). Therefore, drug labeling should identify the approved indication and patient population. Furthermore, it is important to emphasize the following points:

- Product labeling for such drugs should include not only the known risks and benefits of the drug but also a description of the limitations of the available information that supported approval
- It is important for the health care community to be informed on how to use the drug appropriately (i.e., make clear the approved patient population for which the FDA has determined the benefits of the drug outweigh the risks)

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<sup>32</sup> See section 505(d) of the FD&C Act (“[T] the term ‘substantial evidence’ means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for the purposes of the preceding sentence.”). See also the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

<sup>33</sup> See section 505(d)(1) of the FD&C Act.

<sup>34</sup> See 21 CFR 312.80, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses.

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- Postmarketing monitoring (or, in some cases, continued development of the drug) can help to further define the drug's safety and efficacy profile (see the response to Question 11)

For all drugs, but particularly for drugs approved with a smaller safety database, important findings regarding safety may first become apparent in the postmarketing period.

### **13. Is the animal rule an appropriate consideration for a streamlined development program?**

When human clinical effectiveness trials can be conducted, drugs are not eligible for approval under the so-called *animal rule*, a term that refers to the regulatory pathway set forth in 21 CFR 314.600 (or, for biologics, 21 CFR 601.90) for approving drugs when human efficacy studies are not ethical or feasible.

### **14. What is the role of a rapid diagnostic in streamlined antibacterial drug development programs?**

The use of bacterial detection methods, other than culture, may help define the population identified to have a bacterial pathogen. Examples of nonculture detection of bacterial pathogens include urinary antigen tests, serology, and polymerase chain reaction.

The clinical trial for a candidate antibacterial drug may provide an opportunity to contribute to the development and evaluation of a new diagnostic test. Sponsors are encouraged to discuss these approaches with the Division of Anti-Infective Products and the appropriate review division in the Center for Devices and Radiological Health.

The development and use of rapid detection methods should be helpful in identifying patients with the particular pathogen for drugs that have a narrow spectrum of activity (e.g., drugs active against a single species or a few species within a genus).

### **15. Can an antibacterial drug be developed using a streamlined approach for patients with an unmet medical need and subsequently for other indications?**

Yes, a sponsor can use the streamlined development approach to obtain approval of an indication that addresses an unmet medical need, and subsequently develop the drug for other indications. In general, a streamlined approach should not be used for a subsequent indication if the drug was initially developed using a traditional approach.

### **16. Does the approval of one drug for the treatment of a serious bacterial disease in patients with an unmet medical need preclude approval of another drug for the same indication using a streamlined development program?**

No. The approval of an antibacterial drug for the treatment of serious bacterial diseases in patients with unmet medical need does not necessarily preclude the development of a subsequent

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drug for the same or similar indication using a streamlined development program. The subsequent drug may provide options for patients with certain infections in the future as resistance develops, and would be considered to address an unmet medical need. In addition, under the following circumstances, an antibacterial drug may be considered to address an unmet medical need when there is an already approved treatment for the same indication:

- The first drug approved is found to have serious adverse effects in the postmarketing period that significantly affect its assessment of risk and benefit.
- The adverse effects of the first drug could affect its utility in certain subpopulations (e.g., a drug with the potential to cause nephrotoxicity would be a less than ideal choice in a patient with impaired renal function). A subsequent drug with a different adverse effect profile could provide a treatment option for these patients.
- The approval of more than one therapy addresses an emerging or anticipated public health need, such as a drug shortage or the development of antibacterial resistance.

### **17. Are there special considerations for the product labeling?**

The labeled indication for a drug approved under a streamlined development program should reflect the patient population for which the drug is approved (e.g., the patient population with a serious infection caused by a bacterial pathogen for which the patient has limited therapeutic options). The INDICATIONS AND USAGE section should also summarize the limitations of available data that supported the approval (e.g., limited safety data).<sup>35</sup>

The following example represents wording for an indication based on a streamlined development program for patients who have a serious infection in the setting of limited therapeutic options:

*Drug X is indicated, in patients who have limited or no alternative treatment options, for the treatment of [hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, complicated intra-abdominal infections, complicated urinary tract infections (include as appropriate)] caused by the following susceptible microorganism(s): [list the genus and species of the bacterial pathogen(s)]. Approval of this indication is based on [summarize the limitations of available data that supported the approval].*

The FDA intends to issue separate guidance regarding LPAD, including specific labeling requirements.<sup>36</sup>

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<sup>35</sup> Sponsors are obligated to comply with the content and format requirements of labeling for antibacterial drugs under 21 CFR 201.24, 201.56(d), and 201.57. See the guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements*.

<sup>36</sup> See section 506(h)(3)(A) of the FD&C Act (as amended by the 21st Century Cures Act).

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